THE BACTERIOLOGY AND PATHOLOGY OF DIPHTHERIA.

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Presented by the author

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The results of the researches of Loeffler published at the close of the year 1883 may be said to mark the beginning of the new era in the study of diphtheria, and whatever doubt surrounded his first publication regarding the relation to diphtheria of the micro-organism which now bears his name, has now been finally dissipated. The isolation of the Loeffler bacillus by workers in different parts of the world from the local lesions of the disease in many thousands of cases would seem to afford irrefutable evidence of the constancy of the relationship existing between the bacillus and the pathological process. Hence it is that attention has been directed to a consideration of other aspects of the subject than that of the presence or absence of the Loeffler bacillus in primary diphtheria.

The wide divergence of opinions regarding diphtheria which existed prior to the discovery of the bacillus diphtheriæ illustrates with what difficulty every advance in the study of a disease is accompanied so long as its ætiological factor is still unknown. It had long been a well-established fact that by a variety of agents, pseudo-membranes which offered more or less the appearances seen in diphtheria could be produced upon mucous surfaces in man and in animals; but it was at the same time recognized that none of these agents could reproduce the symptom-complex of diphtheria; and none of us are likely to forget the almost interminable discussion which arose as to whether it was primarily a local or a constitutional disease. Nor did the study of its pathology give much assistance in the solution of this question, and only

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* Being the substance of an address delivered on January 8, 1895, before the Alumni Association of the Jefferson Medical College, Philadelphia.
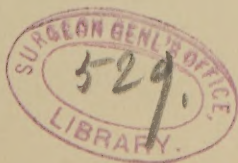
after the specific micro-organism had been obtained in pure culture did it become possible, by a study of its properties outside the body and of its occurrence under natural conditions in human beings, to establish a rational basis for a classification of the disease.

First of all, then, it is important to distinguish between the anatomical and the ætiological significance of the term "diphtheria," and it will be found that a limitation of the term to a disease characterized by the presence of the bacillus diphtheriæ in the affected portion of the body will do much to eliminate the confusion of pathological conditions which, while anatomically resembling one another, are otherwise quite distinct.

The first question to which I would direct your attention regards the proportion of cases of pseudo-membranous inflammations of the throat which are due to the Loeffler bacillus. In the first series reported by Loeffler himself, a certain number of the cases examined did not yield the diphtheritic bacillus; but of these, several were recognized as not having been cases of primary diphtheria. This failure to find the Loeffler bacillus in all pseudo-membranous inflammations in the throat and air-passages has been confirmed by later investigators. Thus in a table prepared by Escherich, in 679 examinations collected from Paris, Berlin and New York, the bacillus diphtheriæ was found in 427, or in 62 per cent. of all the cases. In a series studied by Morse of Boston, of 301 cases examined, the Loeffler bacillus was found in 217, i. e., it was present in 72 per cent. of the cases. Park and Beebe report that of 5611 cases examined, positive results were obtained in 3255 (58 per cent.). The bacillus was absent in 1540 cases (27 per cent.), while 816 cases were doubtful. The doubtful cases represent those in which for some reason or another satisfactory cultures were not supplied. If these, then, be disregarded altogether—although it may not be entirely fair to do this—we find that out of 4795 cases of suspected diphtheria, 68 per cent. were instances of true diphtheria.

It is acknowledged that the pseudo-membranous anginæ which are associated with the acute exanthemata are commonly not caused by the Loeffler bacillus, but are due in most cases to the invasion of the streptococcus pyogenes. In a

series of bacteriological examinations made by Booker in such cases, the bacillus diphtheriæ was constantly absent; and Escherich, who studied fourteen cases of scarlet fever, states that the Loeffler bacillus is never present in the early days of the disease, but that in several of these cases they were found to be present later on, a fact which he attributes to the imperfect separation of diphtheria and scarlet fever patients in the Munich hospital, where his studies were carried on. He also found the Loeffler bacillus in certain cases of measles and whooping-cough, and he agrees with other investigators in holding that the acute exanthematous diseases predispose to infection with the bacillus diphtheriæ.

It had been observed by the older clinicians that during epidemics of diphtheria, pseudo-membranous inflammations of the throat in the course of typhoid fever were more frequent. Morse reports four cases of typhoid fever complicated with diphtheria; at least three of which developed diphtheria after admission to the hospital.

A purely local and perhaps non-contagious inflammation of the larynx has, by the bacteriological examination of a considerable number of cases of membranous croup, been shown to occur unassociated with diphtheria. These cases, however, are quite exceptional. Of 88 cases of membranous croup studied by Martin, 59, or 67 per cent., were of diphtheritic origin. The statistics of Park indicate that in New York fully 80 per cent. of the cases of the same disease are caused by the Loeffler bacillus. Of 229 of Park's cases, in 167 no membrane or exudate was found above the larynx. Welch and Abbott, Booker, Williams, Kolisko and Paltauf, Concietti and Fraenkel have reported cases of laryngeal diphtheria in which the pseudo-membrane was confined to the larynx and lower air-passages.

It is an undoubted fact that a case of so-called membranous laryngitis has not infrequently been the first of a series of cases of genuine faucial diphtheria.

Among the most important results of the bacteriological study of the inflammations of the throat and air-passages has been the discovery that cases which present the features of a mild catarrhal angina or of a lacunar tonsillitis may be associated with the presence of the bacillus diphtheriæ, and that

from these can arise other cases in which membrane is found on the fauces.

This class of cases has been studied by Escherich and Feer, and especially by Koplik. Within the past few weeks I have seen two such instances in the practice of Dr. W. D. Booker, and from them obtained the Loeffler bacilli in cultures. The first was a girl of 16 years, who came to the surgical dispensary of the Johns Hopkins Hospital for enlarged glands of the neck. Upon examination she was found to have a lacunar tonsillitis. She suffered no inconvenience other than that resulting from the swollen glands. The plugs from the crypts of the tonsils contained the Loeffler bacillus. She made a rapid recovery.

The second was a child one and a half years of age whose tonsils were greatly swollen and almost meeting in the middle line of the throat. There was no visible membrane. Cultures from the throat showed the presence of the bacillus diphtheriæ. The local treatment recommended by Loeffler was used, and by the third day all symptoms of the disease had disappeared.

Heubner has just published a short series of cases, in which he calls attention to what he describes under the title of latent diphtheria. These were secondary to other diseases than scarlet fever and measles, and occurred in the young in the course of wasting affections, such as rickets, tuberculosis, etc., in hospital practice. The symptoms were fever, gastrointestinal disturbance, and slight bronchial and nasal catarrh. Heubner says that diphtheritic infection is not apt to be suspected in these cases until laryngeal stenosis suddenly develops, or the fact is revealed at autopsy by the finding of a false membrane in the pharynx or larynx.*

Roux and Martin have found in the course of their inoculation experiments for the preparation of the anti-toxin, that animals which had been previously inoculated with other bacteria or their poisons, from which they had recovered, were more susceptible to the diphtheria toxin ; and, similarly, that pregnant animals or such as had just given birth to young exhibited a similar diminution of resistance.

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*See Flexner and Pease, Johns Hopkins Hospital Bulletin, February, 1895.

The mucous membrane of the nose affords a favorite resting-place for the Loeffler bacillus. In pharyngeal diphtheria these bacilli are commonly present in the nasal secretion, even in the absence of membrane in the nose. Primary diphtheria of the nasal mucous membrane sometimes occurs. Such cases have been reported by Stamm, Baginsky, Abbott, Ravenel, Czemetschka, Townsend and Park. Of the last two writers the membrane was confined to the nose in 4 and 9 cases respectively. Escherich has seen one case in which the infection of the nasal mucous membrane took place through the tear-duct in a case of diphtheritic conjunctivitis. Katz has just reported a case of faucial diphtheria which developed in a child exposed to infection from another child suffering from fibrinous rhinitis due to the Loeffler bacillus.

Babes first cultivated the Loeffler bacillus from the pseudo-membrane in diphtheritic conjunctivitis, and reproduced the disease by the inoculation of the organism upon the conjunctivæ of rabbits. A number of cases of pseudo-membranous conjunctivitis have since been found to be associated with the bacillus diphtheriæ, although it must be stated that not all are caused by this organism. In two cases which I examined for Dr. Hiram Woods the Loeffler bacillus was not found in the exudate, but streptococci were present in both. The results of Councilman's investigations would go to show that certain cases of otitis media are due to this bacillus.

The skin surfaces of the body would appear to be immune to the action of the Loeffler bacillus in the absence of any loss of continuity. Thus Wright cultivated the diphtheria bacillus from excoriated or ulcerated surfaces of the skin in 7 cases of diphtheria; and Park found this organism in wounds of the finger received by physicians while performing intubation. Cases of wound diphtheria associated with the Loeffler bacillus are reported by Brunner, Neisser, Treitel and Abel; but it is probable that most cases of so-called wound diphtheria are caused by other micro-organisms. The relative insusceptibility of the external surfaces of the body to infection with the bacillus diphtheriæ is illustrated by the behavior of tracheotomy wounds, which only exceptionally become infected with this organism. Faltonek examined 953 tracheotomy wounds without succeeding in a single instance in isolating the Loeffler bacillus. Other observers have been

more successful, but in these cases the possibility of the contamination of the wounded surfaces with the tracheal secretion cannot be excluded.

Having now passed in rapid review the situations of common localization of the Loeffler bacillus upon the surface and in the cavities of the body, I would ask your attention to its distribution within the viscera. At the time of Loeffler's first publication he expressed a belief that the bacillus diphtheriæ was to be found only at the local site of the disease, and that it did not invade the tissues at all, or at least only exceptionally. He had cultivated it, however, in one case from the lungs; and later Kolisko and Paltauf and Babes isolated in rare instances a few organisms from the internal organs. The observations of Frosch, since confirmed by others, have shown that not uncommonly a few bacilli enter the circulation and may be cultivated from the internal organs at autopsy. They are not however only small in number, but their distribution is irregular, and it is necessary to transplant considerable quantities of material in order to grow them. Frosch cultivated the bacillus from the blood of the heart, the brain, pleural and pericardial exudates, pneumonic areas in the lungs, spleen, kidneys, bronchial and cervical lymph glands and liver. Booker has also obtained the organism from the internal organs. At the autopsy of a child of three years which had both pharyngeal and laryngeal diphtheria I obtained the bacillus diphtheriæ in pure culture from the heart's blood, cervical lymph glands, liver, spleen, lungs and kidneys, but, contrary to Frosch's experience, they were present, in this case, in large numbers in the blood, glands and spleen. In this as well as in a later instance I was able to cultivate the Loeffler bacillus from bronchopneumonic areas, and also to demonstrate them in sections from the bronchi and lung tissue. The predominating organism, however, was the micrococcus lanceolatus. Kutscher has just shown that the Loeffler bacillus exists at times in considerable numbers and may be the predominating organism in cases of broncho-pneumonia associated with diphtheria, and he inclines to the view that it is capable of causing both bronchitis and consolidation of the lung substance. Wright has found the bacillus diphtheriæ in the internal organs in cases of human diphtheria, and he has also cultivated them

from the liver, spleen, heart's blood and kidneys in a small number of experimental guinea-pigs. Abbott and Ghriskey found that after inoculating cultures of diphtheria bacilli into the testicle of guinea-pigs, small nodules containing this organism sometimes appeared in the omentum; and this bacillus has also been cultivated from the ecchymotic patches in the stomach and from the surface of the membrane in croupous gastritis. Of especial interest is the case reported by Howard, in which a bacillus in all respects resembling the bacillus diphtheriæ, except that it did not possess pathogenic properties for guinea-pigs, was cultivated in large numbers from the heart-valves in a case of acute ulcerative endocarditis and from the infarctions in the spleen and kidneys.

Notwithstanding the results of later and more searching studies which have necessitated a modification of the earlier views regarding the relation of the Loeffler bacillus to diphtheria, and notwithstanding the fact that it is now known that the Loeffler bacillus can develop not only locally upon the affected mucous membrane, it must be considered as proven that only a few organisms penetrate into the body; and there are undoubted instances in which the disease has pursued a typical, severe and even fatal course in which the bacilli have remained localized in the mucous membrane. Hence the local process is still to be regarded as the chief seat of the activity of bacillus diphtheriæ.

The study of the properties of this bacillus as it exists outside the human body and the results derived from the inoculation of susceptible animals would indicate that the effects which it produces upon the body are due to a soluble poison, a toxin, proceeding from its growth and multiplication. By means of this toxin, separated from the living bacilli, all the constitutional effects of diphtheria can be induced. For the production of the false membrane the presence of the bacillus itself is necessary.

The growth and multiplication of the bacilli in the false membrane in the pharynx, larynx and nose are associated with the formation of this toxin, which, entering the body, causes the symptom-complex of the disease. Sidney Martin has extracted from the pseudo-membrane an albumose which possesses the poisonous properties of the toxin.

We owe especially to Roux and Yersin and Brieger and Fraenkel our knowledge of the nature and properties of this toxin. According to their researches it belongs to a class of substances of albuminous nature, possessing poisonous properties, for which the name tox-albumens has been proposed. Up to the present time the tox-albumen of diphtheria has not been obtained in a pure form, but in its impure state it is found to possess extraordinary potency. Susceptible animals (rabbits, guinea-pigs, kittens) inoculated with it exhibit all the symptoms of diphtheria, not excepting the post-diphtheritic paralysis.

The study of the action of this bacillus upon animals has shown a material difference in the virulence exhibited by cultures derived from different colonies, those obtained from a single case showing at times wide variations in virulence. The guinea-pig being the animal most susceptible to its influence, is generally employed for testing these variations.

No less striking are the differences in the potency of the toxin produced by the bacillus, and it has been found that there exists a direct relation between the virulence of the organism and the intensity of the poison which it is capable of yielding.

It cannot be said that any such relation between the virulence of the organism and the severity of the symptoms has been shown to exist for human beings. Indeed, contrary to the results arrived at by Roux and Yersin—which seemed to indicate that a progressive diminution in the virulence of the bacilli corresponding with the mildness of the attack took place, and that the same thing happened during convalescence from a severe attack—Escherich, Tobiesen, and especially Wright, have shown that no such diminution of virulence occurs. Fully as virulent organisms may be found in cases which are mild from a clinical standpoint as in those of severer grade.

The question of individual predisposition or of resistance to the invasion of the bacillus diphtheriæ and to the effects of its toxic products has therefore to be considered in this as in the case of other infectious diseases. What the physical basis for this distinction really is we are probably still far from having discovered. A few of the conditions which favor or

inhibit infection in human beings and in animals seem clear. Hence it is that the results of the recent studies of Wasserman and Abel upon the action of the blood-serum of healthy human beings upon animals previously inoculated with the Loeffler bacillus are suggestive, as they indicate that the serum of certain individuals contains some protecting substance, the power possessed by the serum of adults being greater than that of children.

It is quite established that the bacillus diphtheriæ may possess all grades of virulence down to complete absence of pathogenic power, and some confusion has arisen by the introduction of the term "pseudo-diphtheritic" bacillus to denominate an organism which, while it resembles the true bacillus diphtheriæ, is devoid of virulence for guinea-pigs. This bacillus was first isolated by Hoffmann, who regarded it as identical with Loeffler's bacillus. Roux and Yersin advanced the view that this so-called "pseudo-diphtheritic" bacillus represents an attenuated form of the true bacillus diphtheriæ, and the work of Abbott, Park, Koplik and Escherich lends support to this position. On the other hand, it is suggested that the name "pseudo-diphtheritic" should be reserved to designate bacilli which, though resembling the true diphtheritic bacillus, show certain cultural differences and are devoid of pathogenic effect for guinea-pigs. Such a pseudo-diphtheritic bacillus has been found in a few cases of genuine diphtheria associated with the true bacillus diphtheriæ.

It must be confessed that our knowledge of the relation of the Loeffler bacillus to diphtheria and associated pathological processes has been much extended in the past few years. Thus this organism has been found in a large proportion of all cases of pseudo-membranous inflammation of the throat, and is the probable causative agent in all cases of true diphtheria. Those pseudo-membranous anginæ in which the Loeffler bacillus is not found are characterized in themselves and distinguished from cases of true diphtheria by the mildness of their course, their slightly contagious character and their low mortality; in Park statistics, excluding those associated with scarlet fever, the death-rate was 1.7 per cent.

That virulent diphtheria bacilli may be present upon the mucous membrane of the pharynx without giving rise to a

false membrane is proven by those cases of pure laryngeal diphtheria from which the bacilli have been cultivated from the pharynx. Loeffler found in the throat of a healthy child a bacillus which was identical with the true bacillus diphtheriæ; later Hoffmann, Fraenkel and Feer found it under similar circumstances. In 330 healthy persons examined by Park and Beebe, who gave no history of contact with diphtheria, they found the non-virulent organisms in 24, virulent bacilli in 8, and pseudo-diphtheritic bacilli in 27. The examinations included for the most part children. Of the 8 cases in which virulent bacilli were found 5 were children in an asylum where from time to time true diphtheria occurred. Of the remaining three, one was from a house where a supposed case of croup had existed three weeks before. Two of the 8 children developed diphtheria some days later; the other six remained healthy. Loeffler recently examined the throats of 60 school children and found diphtheria bacilli in four. Of these two subsequently developed diphtheria, one a slight inflammation of the throat, the fourth remaining well.

The study by Park of the throats of persons exposed to diphtheria has shown that in 50 per cent. virulent Loeffler's bacilli are present. Of these 40 per cent. developed later the lesions of the disease. Park states that in the families from which his statistics covering this point were obtained the conditions for the transmission of the disease were most favorable. On the other hand, in families where the patient suffering from diphtheria had been well isolated, the bacilli were found in less than 10 per cent. of the healthy children.

Considered in the light of our present knowledge of the common existence of pathogenic micro-organisms, such as streptococci, staphylococci and pneumococci, in the mouths of healthy persons without necessarily doing harm there, these facts of the occasional occurrence of virulent diphtheria bacilli in the throats of healthy persons are less surprising. Doubtless it is necessary that a certain susceptibility to their action—a predisposition, if you prefer, must exist before their peculiar effects can be exerted. I beg to recall in this place the experimental results obtained from healthy human blood-serum as bearing upon this point. However, the figures furnished by Park and Loeffler would indicate that the pres-

ence of the bacillus diphtheriæ in the throat is far more significant even for the individual himself, to leave out of consideration for a moment those with whom he may come in contact, than are the other pathogenic organisms mentioned.

The bacteriological study of convalescent cases shows that virulent bacilli may persist for a time after the disappearance of the false membrane. They are not uncommonly present after 2 to 3 weeks, and in a few instances they have been found after a much longer period. In a case reported by Park, and one also by Abel, they were still demonstrable on the 56th and 65th day respectively after the membrane had entirely gone.

The severity of the case has no influence upon the duration of the presence of the bacilli; the occurrence of nasal diphtheria as a complication seems to favor this persistence. Tezenas found in 12 cases complicated with nasal diphtheria that for a long time after the membrane had disappeared a serous exudation from the nose continued. In ten of these cases Loeffler bacilli were demonstrable so long as the secretion persisted, although they had long ceased to be present in the throat. Hence where cultures cannot be made it is recommended to continue the isolation of the patients for at least three weeks after the disappearance of the membrane.

It is probable that the bacillus diphtheriæ is capable of increasing only within the body of infected persons or in the seat of inoculation of susceptible animals. The bacilli are, however, able to remain alive and in a condition capable of causing infection for a considerable time when outside the body. Conditions which promote the drying of the organism and exposure to strong light are unfavorable for the preservation of its vitality. The individual Loeffler bacilli quickly die when allowed to become air dry. But in bits of mucus or membrane, particularly if protected from the light and preserved in a damp place, they may remain alive for a long time—upon old cultures from 5 to 15 months; in bits of membrane from 4 to 17 weeks. They have been cultivated from tableware and toys; from soiled linen which had been in contact with the sick; from the shoes and hair of nurses, and from the broom used to sweep the floor of a diphtheria ward. In view of these facts it is unnecessary to point out

the importance of thorough disinfection and of the rigorous care that should be observed in disposing of the excreta of the sick.

The association of other micro-organisms with the bacillus diphtheriæ in the false membrane is by no means uncommon, although cases of pure diphtheritic pseudo-membranous inflammations are said to exist. The organisms usually associated with the Loeffler bacillus are the pyogenic cocci, strepto-, staphylo- and diplococci. Their presence is now known to be of great clinical and pathological significance, especially if they enter the deeper tissues, as they are wont to do. While the bacillus diphtheriæ is found only exceptionally in the adjacent lymph glands and internal organs, there exists a group of cases of poly-infection, especially with streptococci, in which the latter enter the circulation and invade the organs. Since the introduction of the anti-toxin treatment of diphtheria this class of cases has attracted especial attention. These cases had been recognized and studied by a number of investigators, and in this country especially by Councilman and his associates. Broncho-pneumonias, suppurations of lymph glands and septic forms of diphtheria are attributed to these associated bacteria, particularly to the streptococcus. Roux and Yersin first pointed out the importance of this poly-infection, and subsequently Schreider, Mya, Barbier and Martin confirmed their observations. Funk, Roux and Martin and Bernheim have recently made careful experimental studies on this subject. The latter employed only organisms which had been associated in the diphtheritic membrane, and he found that the virulence of the Loeffler bacillus is increased both by being grown with the streptococcus or in the filtrate obtained from streptococcus cultures. A limited number of experiments with staphylococci did not show a similar increase in the virulence of the bacillus diphtheriæ, a result confirmatory of Mya's earlier experiments. On the other hand, in human beings, according to Morse's statistics, cases of poly-infection with staphylococci run a more unfavorable course than those with streptococci. Welch has criticized his conclusions and shown the improbability of their correctness.

The natural variation in virulence of the bacillus diphtheriæ led first unintentionally, and later purposely, to the

rendering of animals immune to subsequent inoculation to the Loeffler bacillus. But it was soon observed that this method of securing immunity was capricious and unreliable. The use of cultures of bacilli attenuated by chemical agents, the injection of tissue fluids into another of an animal dead of a previous inoculation of the bacilli, the employment of sterilized bouillon cultures and of cultures grown in infusions of cellular organs, such as the thymus gland, while attended with success in some cases, were found to be precarious methods of securing immunity, and not at all adapted to large animals. The use of a virus obtained from bouillon cultures several weeks old by filtration has been successfully employed by Behring, Ehrlich and Wasserman, Roux and others, to render even large animals such as the horse immune to large doses of diphtheria cultures. And one of the surprising and significant facts which has resulted from the study of the changes induced in the body fluids of the immune animal consists in the discovery that they contain a substance which is capable of rendering other animals, and even human beings, immune from diphtheria and also of curing the disease after its development.

This anti-toxin obtained from the blood of immune animals, though antidotal to the poison of the bacillus diphtheriæ, exerts no power over the poison produced by the bacteria associated with the Loeffler bacillus in the pseudo-membrane, and thus it becomes clear why cases of poly-infection are less influenced by the anti-toxin treatment than those of pure diphtheria.

It is but a confirmation of an intuitive belief to find that in the blood of human beings well of diphtheria there exists a body similar to that found in immune animals. The experiments of Klemenciwicz and Escherich proved the correctness of this supposition, and Abel has just furnished a large series of observations with confirmatory results. In animals a certain time elapses after the inoculation of the toxin before the anti-toxin appears, and it is only after repeated doses at intervals that a high grade of anti-toxic power is developed in the blood-serum. In human beings the blood taken on the 5th or 6th day after infection shows no protective action ; the protecting power appears from the 8th to the 11th day, and it persists a

variable time. Sometimes it fails to appear at all. After some months it may be still present, though in a diminished degree, or it may have entirely disappeared. The longest periods of its persistence yet observed are 150 and 200 days.

These facts bear out the experience of physicians who have noted that diphtheria is not one of those diseases one attack of which affords protection to subsequent infection. Perhaps the individual differences observed are to be explained by the variation in the amount of healing and protecting substances formed in any case.

In cases of genuine diphtheria the Loeffler bacilli are found in large numbers in the pseudo-membrane, there being less in the deeper than in the older and more superficial parts. A lesion of the surface provides a condition favorable to their settlement and increase, a fact also borne out by experiments on susceptible animals. Where no previous defect exists it is probable that the toxin itself can cause a superficial lesion. The tonsils, which are the starting-points of many cases of diphtheria, afford an excellent nidus for the bacilli, on account of the incompleteness of their epithelial covering, even in health. The depth and extent of the necrosis of the mucous membrane vary in different cases; and the character of the pseudo-membrane is affected by the nature of the underlying structures; in the pharynx it is firmer and less easily separable than in the larynx and trachea, where a distinct basement membrane is found in the mucosa.

The earlier workers in the field of experimental diphtheria failed to find in the internal organs the lesions which had been described by Oertel in the tissues of human beings dead of diphtheria. These lesions consist of foci of cell-death characterized by extensive destruction and fragmentation of cell nuclei. In such areas of necrosis fibrin may be deposited. Dr. Welch and I confirmed and extended these results of Oertel by experiments upon guinea-pigs, kittens and rabbits. Subcutaneous inoculation of cultures of the organism or of the filtrate in a bouillon culture 4 or 5 weeks old, produces, besides the local lesion peculiar to each, foci of cell-death in the adjacent lymph glands and in the lymph glands throughout the body; in the spleen, liver, lungs, heart muscle and intestinal mucosa. The kidneys show degenerative changes.

When the dose is small and the animal lives several weeks the paralysis which belongs to the disease may develop. This phenomenon, first observed in animals by Roux and Yersin, was noticed among our animals. Interesting changes have been described in the peripheral nerves under these conditions by Sidney Martin. In some cases he observed defects in the myeline sheaths, which stained poorly in osmic acid, while in certain severe cases the sheaths had entirely disappeared. The axis cylinders were either intact or had undergone granular degeneration, and the continuity of some of the fibres had become broken. At times the muscles supplied by these nerves showed signs of fatty degeneration. These changes agree with those found by Gombault, Meyer, Leyden and Arnheim in human beings who had suffered from diphtheritic paralysis.

Albuminuria is a not infrequent complication of the disease, and casts may appear in the urine. In some cases the urine may be much diminished in amount, but uræmia is unusual; and hydrops, which seldom occurs, is, when present, of a mild grade. The heart is not uncommonly involved, and the lesions described are either parenchymatous degeneration, in the severer grades, associated with fatty degeneration, or interstitial myocarditis. The lymphatic glands of the neck become swollen, but show a slight tendency only to suppuration. Various complications due to the invasion of secondary micro-organisms occur.